General

Guideline Title

Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition.

Bibliographic Source(s)

Watson H, Davidson S, Keeling D. Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. Br J Haematol. 2012 Dec;159(5):528-40. PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Keeling D, Davidson S, Watson H, Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The management of heparin-induced thrombocytopenia. Br J Haematol 2006 May;133(3):259-69.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Incidence, Clinical Presentation and Platelet Monitoring

- Patients who are to receive any heparin should have a baseline platelet count (2C).
- Post-operative patients, including obstetric cases, receiving unfractionated heparin (UFH) should have platelet count monitoring performed every 2 to 3 days from days 4 to 14 or until heparin is stopped (2C).
- Post-cardiopulmonary bypass patients receiving low-molecular-weight heparin (LMWH) should have platelet count monitoring performed every 2 to 3 days from days 4 to 14 or until heparin is stopped (2C).
- Post-operative patients (other than cardiopulmonary bypass patients) receiving LMWH do not need routine platelet monitoring (2C).
- Post-operative patients and cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 days and are receiving any type of heparin should have a platelet count determined 24 h after starting heparin (2C).
- Medical patients and obstetric patients receiving heparin do not need routine platelet monitoring (2C).
- If the platelet count falls by 30% or more and/or the patient develops new thrombosis or skin allergy or any of the other rarer manifestations of heparin-induced thrombocytopenia (HIT) (see Table II in the original guideline document) between days 4 and 14 of heparin administration HIT should be considered and a clinical assessment made (2C).
- HIT can be excluded by a low pre-test probability score without the need for laboratory investigation (2B).
- If the pre-test probability of HIT is not low, heparin should be stopped and an alternative anticoagulant started in full dosage whilst

laboratory tests are performed (1C).

Laboratory Tests

- Platelet aggregation assays using platelet-rich plasma (PRP) lack sensitivity and are not recommended (2C).
- Platelet activation assays using washed platelets (heparin-induced platelet activation assay [HIPA] and serotonin release assay [SRA]) have a higher sensitivity than platelet aggregation assays using PRP and are regarded as the reference standard, but are technically demanding and their use should be restricted to experienced laboratories (2C).
- Non-expert laboratories should use an antigen assay of high sensitivity. Only the immunoglobulin G (IgG) class needs to be measured. Useful information is gained by reporting the actual optical density (OD), degree of inhibition by high dose heparin, and the cut-off point for a positive test, rather than simply reporting the test as positive or negative (1B).
- In making a diagnosis of HIT, the clinician's estimate of the pre-test probability of HIT, together with the type of assay used and its quantitative result (enzyme-linked immunosorbent assays [ELISA] only) and information on reversal using higher doses of heparin should be used to determine the post-test probability of HIT (2B).
- HIT can be excluded in patients with an intermediate pre-test score who have a negative particle gel immunoassay (2B).
- HIT can be excluded in all patients by a negative antigen assay of high sensitivity (1A).

Treatment

General Principles

- Clinical decisions should be made following consideration of the risks and benefits of treatment with an alternative anticoagulant (1C).
- For patients with suspected (non-low pre-test probability) or confirmed HIT, heparin should be stopped and full dose anticoagulation with an alternative anticoagulant commenced (1B).
- LMWH should not be used in the treatment of HIT (1A).
- Warfarin should not be used until the platelet count has recovered to the normal range. When introduced, an alternative anticoagulant must be continued until the international normalized ratio (INR) is therapeutic. Argatroban affects the INR and this needs to be considered when using this drug. A minimum overlap of 5 days between non-heparin anticoagulants and vitamin K antagonist (VKA) therapy is recommended (1B).
- Platelets should not be given for prophylaxis (1C) but may be used in the event of bleeding (2C).
- If the patient has received a VKA at the time of diagnosis it should be reversed by administering intravenous vitamin K (2C).

Alternative Anticoagulants

- Danaparoid in a therapeutic dose regimen is a suitable alternative anticoagulant for use in patients with HIT (1B).
- Danaparoid at prophylactic doses is not recommended for the treatment of HIT (1B).
- Monitoring the anticoagulant effect of danaparoid using an anti-Xa assay with specific danaparoid calibrators should be considered in patients >90 kg and in patients with renal impairment (glomerular filtration rate <30 ml/min) (2C).
- An argatroban infusion adjusted to an activated partial thromboplastin time (APTT) ratio of 1.5–3.0 (but not exceeding 100 s) is a suitable alternative anticoagulant for the treatment of patients with HIT (1C).
- Patients on argatroban undergoing transition to warfarin should have an INR ≥4 for 2 days prior to discontinuing argatroban (2C).
- Therapeutic dose fondaparinux is an acceptable alternative anticoagulant for managing HIT but it is not licensed for this indication (2C).
- Patients should be therapeutically anticoagulated for 3 months after HIT with a thrombotic complication (1A) and for 4 weeks following HIT without a thrombotic complication (2C).
- Women with HIT in pregnancy should be treated with a non-cross reacting anticoagulant. Danaparoid should be used where available and fondaparinux also considered (2C).

Anticoagulation in Patients with a History of HIT

Cardiac Surgery

- Patients with previous HIT who are antibody negative (usually so after >100 days) who require cardiac surgery should receive intra-operative UFH in preference to other anticoagulants, which are less validated for this purpose. Pre- and post-operative anticoagulation should be with an anticoagulant other than UFH or LMWH (1B).
- Patients with recent or active HIT should have the need for surgery reviewed and delayed until the patient is antibody-negative if possible. They should then proceed as above. If deemed appropriate, early surgery should be carried out with an alternative anticoagulant (1C).
- As an alternative anticoagulant in cases where urgent surgery is required we suggest bivalirudin (2B).

Percutaneous Coronary Intervention

- In patients with previous or present HIT who require coronary intervention including angiography and percutaneous coronary intervention the Task Force recommends the use of bivalirudin (2B)

Definitions:

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Heparin-induced thrombocytopenia (HIT)
- HIT with thrombosis

Guideline Category

Diagnosis

Evaluation

Management

Screening

Treatment

Clinical Specialty

Cardiology

Critical Care

Emergency Medicine

Family Practice

Hematology

Internal Medicine

Obstetrics and Gynecology

Pathology

Surgery

Thoracic Surgery

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide healthcare professionals in the United Kingdom with clear guidance on the clinical features of heparin-induced thrombocytopenia (HIT), the indications for monitoring of patients on heparins for HIT, the investigation of suspected HIT and the treatment of HIT

Target Population

- All patients who receive heparins
- Patients with suspected or confirmed heparin-induced thrombocytopenia (HIT)
- Patients with previous HIT who are antibody negative who require cardiac surgery or who require coronary intervention including angiography and percutaneous coronary intervention

Interventions and Practices Considered

Diagnosis/Evaluation/Screening

1. Platelet count in patients receiving heparins
2. Timing of platelet counts
3. Calculating pre-test probability score of heparin-induced thrombocytopenia (HIT)
4. Laboratory tests
    - Platelet activation assays using washed platelets (heparin-induced platelet activation assay [HIPA] and serotonin release assay [SRA])
    - Platelet aggregation assays using platelet rich plasma

- Antigen assays for IgG class of antibodies
- Quantitative results for enzyme-linked immunosorbent assay

Management/Treatment

1. Heparin alternative anticoagulants in patients with suspected or confirmed HIT
    - Danaparoid
    - Fondaparinux
    - Argatroban
    - Warfarin
2. Monitoring of anticoagulant therapy (anti-Xa assay, activated partial thromboplastin time [APTT], international normalized ratio [INR])
3. Anticoagulation in patients with previous or active HIT who require cardiac surgery (bivalirudin)

Major Outcomes Considered

- Sensitivity and specificity of laboratory tests
- Clinical outcomes, including new thrombotic events, amputation, or death
- Pregnancy outcome
- Major bleeding

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The 2006 guideline was reviewed along with additional information published since 2005. A search was performed of PubMed and EMBASE using the term 'heparin induced thrombocytopenia' combined with 'diagnosis', 'treatment' and 'clinical presentation'. The search covered articles published from January 2006 to April 2012. References in recent reviews were also examined.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to quote levels and grades of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline was drafted by a writing group identified by the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH). The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the BCSH.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 UK haematologists, the British Committee for Standards in Haematology (BCSH), and the British Society for Haematology Committee and comments incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate recognition of and management of heparin-induced thrombocytopenia

Potential Harms

- Warfarin, especially when used in isolation, can increase the risk of microvascular thrombosis in heparin-induced thrombocytopenia (HIT) and its introduction should be delayed until there has been substantial resolution of the thrombocytopenia. It should then be introduced with overlap of the alternative anticoagulant. Where argatroban is being used care is required in the interpretation of the international normalized ratio (INR).
- There is some residual concern that platelet transfusions could theoretically contribute to thrombotic risk. Based on this, it is reasonable to consider platelet transfusion for patients with HIT and bleeding but prophylactic platelet transfusion is generally not advised.

Contraindications

Contraindications

Argatroban requires no dose adjustment in renal failure but it is contraindicated in severe hepatic failure and expert opinion suggests dose adjustment in critically ill patients in the intensive care setting.

Qualifying Statements

Qualifying Statements

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Safety

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 May (revised 2012 Dec)

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

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Guideline Availability

Electronic copies: Available from the British Committee for Standards in Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 22, 2008. This summary was updated by ECRI Institute on July 27, 2010 following the FDA drug safety communication on Heparin. This NGC summary was updated by ECRI Institute on January 15, 2013.

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